REMARKS

No claims have been added. Claims 1, 6-10, 12, 21-25 and 27 are being cancelled. Claims 11, 13, 15-22, 26, 28-31 and 44 are being amended. Upon entry of this amendment, claims 2, 5, 11, 13-23, 26, 28-31, 42 and 44 will be pending in the application.

This amendment is being filed with a Request for Continued Examination under 37 C.F.R. 1.114. This Response and amendment is the submission required under these Rules.

Claim 11 is being made independent. This amendment is supported by claim 6 from which it depended.

The amendment to claims 13, 15-16 and 30 removes moieties that were asserted to be outside of the elected group under consideration.

The amendment to claims 15-16 clarifies that the T_1 moiety is optionally substituted.

The amendment to claims 2, 5, 17-19 changes dependency.

The amendment to claim 20 removes allegedly unclear text from the preamble, removes moieties that were asserted to be outside of the elected group under consideration and adds moieties. The added moieties are supported by the specification at, for example, pages 8-13.

The amendment to claim 26 clarifies the preamble, removes moieties that were asserted to be outside of the elected group under consideration and clarifies that the T_1 moiety is optionally substituted.

The amendment to claim 31 removes moieties that were asserted to be outside of the elected group under consideration and clarifies that the T_1 moiety is optionally substituted.

The amendment to claim 44 clarifies that cannabinoid receptor includes at least one of the CB1 or CB2 cannabinoid receptors. This amendment is supported by the specification at, for example, pages 34-36 and Table 3.

The Objection to Claims 1-31 as containing non-elected subject matter

The Office communication objects to claims 1-31 as containing non-elected subject matter.

The Office communication on page 2 indicates that the elected group comprises compounds exemplified by compounds 9-16 in Applicant's table 1 wherein W represents C=O, Z represents O, Y represents N (since N is not a possibility Applicant takes this to mean a N containing moiety), R2 represents O (since O is not a possibility Applicant takes this to mean an O containing moiety), R1 represents substituents other than H and ring C is aromatic. Applicant has amended the claims to conform to the Examiner's instructions as best understood.

Claim Rejections Under 35 U.S.C. §112 Second Paragraph

The previous Office communication rejected claims 1-31 under 35 U.S.C. §112, second paragraph, as being indefinite or failing to particularly point and distinctly claim the subject matter which the Applicant regards as the invention. Specifically, that Office communication stated that:

> In claims 1-31, the values of all variables defined as ----comprising---- is indefinite since it is not clear whether these substituents are attached directly or indirectly to the tricyclic ring system. . . .
> In claim 1, it is not clear what is being used to excite the cannabinoid compound? Also is this method *in vivo* method or *in vitro* method?
> In claims 3, 4 and 20, the values of variables X, Z, R2, R3, R4 and R5 are not defined.
> In claim 3, the value of variable Y defined as ---electron rich element--- is indefinite since this element is not defined.
> In claim 17, the term ---sample--- is indefinite since its meaning is not clear.
> In claims 18 and 19, the term ---interacting is indefinite since its meaning is not clear. Also, which receptor subtype is being interacted?
> In claim 20, it is not clear how the fluorescent property is detected.
> Claim 1 provides for the use of fluorescent cannabinoid compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The present Office communication indicates that these rejections of record have been maintained. The present Office communication also states:

> In claims 1,2 and 5, the values of variables R1-R5 is not defined.
> In claims 6 and 11-20, it is not clear what is being used to excite the cannabinoid compound? Also, is this method in vivo or in vitro method?
> In claims 43 and 44, it is not clear which specific cannabinoid receptor is being stimulated and furthermore, how this stimulation is being assessed in vivo? What happens following stimulation of the cannabinoid receptor?

Applicant respectfully reminds the Examiner that "[t]he requirement that the claims 'particularly point out and distinctly claim' the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when read in conjunction with the rest of the specification. 'If the claims read when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." "A claim is not 'indefinite' simply because it is hard to understand when viewed without the benefit of the specification." S3 Inc. v. Nvidia Corp., 259 F.3d 1364, 59 U.S.P.Q.2d 1745 (Fed. Cir. 2001).

Use of Word "Comprising" in Claim 11 has been changed.

Claim 11 was inadvertently not amended in the previous Response to replace the term comprising in the preamble. Applicant has amended claim 11 to replace the term "comprising" in the preamble. As such, any proper rejection of claim 11 under 35 U.S.C. §112, second paragraph has been obviated.

rejections involving claim 1 have been obviated.

Claim 1 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 1 is obviated by this cancellation.

variables X, Z, R2, R3, R4 and R5 in claims 2-5 and 20 have been defined.

Claims 3-4 have been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claims 3-4 is obviated by this cancellation.

Claims 2 and 5 have been amended to depend from claim 6. Claim 6 recites values for variables X, Z, R2, R3, R4 and R5. Any proper rejection of claims 2 and 5 is obviated by this amendment.

Claim 20 has been amended to recite values for variables X, Z, R2, R3, R4 and R5. Any proper rejection of claim 20 is obviated by this amendment.

use of electron rich element in claim 3 has been obviated.

Claim 3 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 3 is obviated by this cancellation.

the word "sample" in claim 17 is clear in view of at least the specification and knowledge in the chemical art.

The Office communication asserts that the term "sample" in claim 17 is "indefinite since its meaning is not clear". The previously submitted page from Webster's New Collegiate Dictionary, 1974 ed., defines sample as: "a representative part of a single item from a larger whole or group presented for inspection . . .". The previously submitted page from McGraw-Hill Dictionary Of Scientific And Technical Terms, 1989 ed., defines sample as: "representative fraction of material tested or analyzed . . ." Further, the concept of samples and sampling is well understood in the scientific arts and is taught to students at grade school levels.

As another example, Applicant directs the Examiner's attention to the previously submitted Biochemical Calculations, page 347 where it is discussed a sample "**might be** (emphasis added) diluted urine, or serum, or an enzyme mixture containing organic buffers".

These definitions and concepts are further supported by Applicant's specification.

For example, reference to test samples in conjunction with the techniques[1] disclosed on page 24; and "biopsy samples", page 27, line 25. See also Applicant's specification at page 34, line 2 to page 35, line 29 wherein some compounds are combined with samples to provide cannabinoid receptor binding data.

Clearly one skilled, or even relatively unskilled, in the chemical art would understand the phrase sample. Although the term and concept of a sample appears clear, Applicant has amended claim 17 to recite test sample. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

claims 18 and 19 are clear in view of at least the specification and knowledge in the art.

The Office communication states that the term "interacting" is "not clear". Applicant respectfully directs the Examiner's attention to page 25, line 6-8 of the specification, which gives an example of the term "interacting". As illustratively recited by this passage, "[t]he inventive cannabinoid agonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to initiate a physiological or a pharmacological response characteristic of that receptor." One skilled in the relevant art would understand the term "interacting". Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

- claim 20 no longer recites the word detecting.

Claim 20 has been amended so that the phrase "for detecting a fluorescent property" is no longer recited. Any proper rejection of claim 20 on the basis of clarity of detection of the fluorescent property is obviated by this amendment.

[1] Fluorescence Microscopy, Fluorescence Polarization Spectroscopy, Fluorescence Resonance Energy Transfer Analysis, Flow Cytometry, Fluorescence Photo-Bleach, Immunofluorescence, and Fluorescent Competitive Binding Assay. It should be understood that the present method encompasses use of the inventive compounds in any technology wherein their fluorescent properties are desirable. Thus, the inventive fluorescent cannabinoids can be employed as Fluorescent Molecular Probes, Fluorescent Imaging Agents, Fluorescent Control Standards and Cellular Markers in a broad scope of biomedical research involving cannabinoid receptors. In addition, the fluorescent cannabinoids can be applied in clinical use as Fluorescent Diagnostic Agents to determine therapeutic drug levels and the presence of drugs of abuse in fluids.

- claims 6 has been cancelled without prejudice and claims 11-19 more clearly recite that the cannabinoid compound is excited with electromagnetic radiation.

Claim 6 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 6 is obviated by this cancellation.

Claim 11 has been amended to more clearly recite that the cannabinoid compound is excited with electromagnetic radiation. Any proper rejection of claim 11, or claims dependent therefrom, on this basis is obviated by this amendment.

Claim 20 does not recite that anything is excited. Applicant respectfully traverses this rejection of claim 20.

Claims 6 and 11-20 can be used both in vivo and in vitro.

Claim 6 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 6 is obviated by this cancellation.

Claim 20 recites a "test kit comprising a cannabimimetic compound having an endogenous fluorescent property" and a specified structure. Claim 20 is NOT directed to a method. Applicant respectfully traverses this rejection.

As discussed in more detail below, the method of claim 11 can be used in vitro or in vivo. In vitro fluorescence is exemplified in Applicant's specification, for example in Table 2. Enclosed herewith is an abstract from Capasso R. et al, Fatty acid amide hydrolase controls mouse intestinal motility in vivo, Gastroenterology, 2005 Sept., 129(3) 941-951. Applicant has not been able to obtain a copy of the original article. That abstract is believed to disclose use of fluorescent compounds, and fluorescence methods, in mouse small intestine in vivo. In vivo fluorescence methods are known as shown by the enclosed abstract. Applicant respectfully traverses this rejection of claim 20.

Claim 44 refers to at least one of the CB1 and CB2 cannabinoid receptors.

Claim 43 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 43 is obviated by this cancellation.

Claim 44 has been amended to more clearly recite stimulation of at least one of the CB1 and CB2 cannabinoid receptors. Any proper rejection of claim 44 on this basis is obviated by this amendment.

Claim 44 and in vivo stimulation.

Claim 43 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 43 is obviated by this cancellation.

Some of Applicant's compounds have been tested in vitro for binding affinity to cannabinoid CB1 receptors (derived from rat forebrain membranes) and also for binding affinity to cannabinoid CB2 receptors (derived from mouse spleen). See Applicant's specification at page 34, line 2 to page 35, line 33. Applicant's tested compounds, for example compound 15, are shown to have an affinity to bind to CB1 and/or CB2 cannabinoid receptors when tested in vitro. See Table 3 on page 36. Thus, some of Applicant's compounds are shown to bind to cannabinoid receptors present in animal brain (CB1) and peripheral (CB2) tissues. If the compounds can bind to these receptors in vitro, they are typically expected to bind to the same receptors in vivo.

It is well known that compounds that bind to a receptor in an individual or animal can also stimulate or modulate that receptor to provide a physiological response in that individual or animal. Some examples of such modulation are discussed in Applicant's specification at page 28, line 22 to page 29, line 8.

Applicant is also submitting herewith a test report showing a test method and results. The test report illustrates that compound 15 when tested in vivo produces an antinociceptive effect (inhibition of the perception of pain) in male rats. This effect was assessed in vivo. Thus, cannabinoid receptor stimulation by Applicant's claimed compounds can be assessed either in vitro or in vivo.

The art recognizes use of fluorescent compounds and fluorescence methods in vivo.

Enclosed herewith is an abstract from Capasso R. et al, Fatty acid amide hydrolase controls mouse intestinal motility in vivo, Gastroenterology, 2005 Sept., 129(3) 941-951. That abstract is believed to disclose use of fluorescent compounds, and fluorescence methods, in mouse small intestine in vivo.

Claim 44 and events subsequent to stimulation of the cannabinoid receptor.

Claim 43 has been cancelled without prejudice and only to progress prosecution of this application. Any proper rejection of claim 43 is obviated by this cancellation.

Claim 44 does NOT claim anything other than stimulation of at least one of the cannabinoid receptors. Such stimulation is supported by Applicant's specification at, for example, Table 3, which clearly discloses stimulation of CB1 and/or CB2 cannabinoid receptors and the enclosed test report for compound 15. Applicant respectfully asserts that claim 44 is definite and supported as amended and traverses this rejection.

In summary, Applicants have addressed each of the objections and rejections within the present Office Action. It is believed the application now stands in condition for allowance, and prompt favorable action thereon is respectfully solicited.

The Examiner is invited to telephone Applicant(s)' attorney if it is deemed that a telephone conversation will hasten prosecution of this application.

Respectfully submitted,

Alexandros Makriyannis et al

By: _____
James E. Piotrowski
Registration No. 43,860
Alix, Yale & Ristas, LLP
Attorney for Applicants

Date: 11-16-2005
750 Main Street- Suite 1400
Hartford, CT 06103-2721
(860) 527-9211

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Result of *in vivo* test for compound 15 (AM792)

Previous studies have suggested that analgesia can be obtained through activation of CB2 cannabinoid receptors.[1] One of the keto cannabinoids, compound **15,** showing significant selectivity for the CB2 receptors (K_i = 0.4 nM) was tested by an *in vivo* assay for the ability to generate antinociceptive effect by stimulation of cannabinoid receptors.

Methods. Male Sprague-Dawley rats (Harlan; Indianapolis, IN) 200 - 300 grams at time of testing, were maintained in a climate-controlled room on a 12-h light/dark cycle (lights on at 06:00 h) and food and water were available ad libitum. All of the testing was performed in accordance with the policies and recommendations of the International Association for the Study of Pain (IASP) and the National Institutes of Health (NIH) guidelines for the handling and use of laboratory animals. The drug was dissolved in dimethyl sulfoxide (DMSO) and were injected subcutaneously in the plantar surface of the hindpaw in a total volume of 50 µl. DMSO given in hindpaw at this volume had no effect. The method of Hargreaves et al[2] was employed to assess paw-withdrawal latency to a thermal nociceptive stimulus. Rats were allowed to acclimate within a plexiglass enclosures on a clear glass plate maintained at 30°C. A radiant heat source (i.e., high intensity projector lamp) was activated with a timer and focused onto the plantar surface of the hindpaw. Paw-withdrawal latency was determined by a photocell that halted both lamp and timer when the paw was withdrawn. The latency to withdrawal of the paw from the radiant heat source was determined both before and after drug or vehicle administration. A maximal cut-off of 40 sec was employed to prevent tissue damage.

Effects. The A_{50} (dose producing a 50% antinociceptive effect) was 2.67 mg/kg (95% confidence limits = 2.03-3.53 mg/kg) for compound **15**.

1. Malan, T. P.; Ibrahim, M. M.; Deng, H.; Liu, Q.; Mata, H. P.; Vanderah, T. W.; Porreca, F.; Makriyannis, A. CB_2 Cannabinoid Receptor-Mediated Peripheral Antinociception. *Pain* 2001, *93*, 239-45.
2. Hargreaves, K.; Dubner, R.; Brown, F.; Flores, C.; Joris, J. A New Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia. *Pain* **1988**, *32*, 77-88.

1. Capasso R, Matias I, Lutz B, Borrelli F, Capasso F, Marsicano G, Mascolo N, Petrosino S, Monory K, Valenti M, Di Marzo V, Izzo AA. Fatty acid amide hydrolase controls mouse intestinal motility in vivo. Gastroenterology. 2005 Sep;129(3):941-51.

Abstract:
BACKGROUND & AIMS: Fatty acid amide hydrolase (FAAH) catalyzes the hydrolysis both of the endocannabinoids (which are known to inhibit intestinal motility) and other bioactive amides (palmitoylethanolamide, oleamide, and oleoylethanolamide), which might affect intestinal motility. The physiologic role of FAAH in the gut is largely unexplored. In the present study, we evaluated the possible role of FAAH in regulating intestinal motility in mice in vivo. METHODS: Motility was measured by evaluating the distribution of a fluorescent marker along the small intestine; FAAH messenger RNA (mRNA) levels were analyzed by reverse-transcription polymerase chain reaction (RT-PCR); endocannabinoid levels were measured by isotope-dilution, liquid chromatography, mass spectrometry. RESULTS: Motility was inhibited by N-arachidonoylserotonin (AA-5-HT) and palmitoylisopropylamide, 2 selective FAAH inhibitors, as well as by the FAAH substrates palmitoylethanolamide, oleamide, and oleoylethanolamide. The effect of AA-5-HT was reduced by the CB1 receptor antagonist rimonabant and by CB1 deficiency in mice but not by the vanilloid receptor antagonist 5'-iodoresiniferatoxin. In FAAH-deficient mice, pharmacologic blockade of FAAH did not affect intestinal motility. FAAH mRNA was detected in different regions of the intestinal tract. CONCLUSIONS: We conclude that FAAH is a physiologic regulator of intestinal motility and a potential target for the development of drugs capable of reducing intestinal motility.